JOC Article

# Solid-Phase Synthesis of 5-Isoxazol-4-yl-[1,2,4]oxadiazoles

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A library of isoxazole and 1,2,4-oxadiazole-containing diheterocyclic compounds has been prepared. Our strategy was explored in solution phase first as follows. PMB-protected 3-butyn-2-ol was deprotonated with *n*BuLi, acylated with methyl chloroformate, and then employed in a nitrile oxide 1,3-dipolar cycloaddition (benzaldehyde oxime in the presence of bleach) to afford the isoxazole-substituted carboxylic acid methyl ester. Ester saponification with aqueous NaOH followed by a two-step condensation with benzamidoxime gave the final isoxazole-oxadiazole diheterocyclic product in good yield. With some modifications, we next explored this chemistry on Wang resin, which led to 18 final products that were cleaved from polymer beads with 50% TFA in dichloromethane.

## Introduction

The synthesis of highly functionalized libraries of organic molecules using solid-phase organic synthesis methodology is recognized as a valuable tool for drug discovery. The isoxazole ring system, which is typically prepared by the 1,3-dipolar cycloaddition of a nitrile oxide to an alkyne, is particularly interesting since it is readily transformed into various biodynamic agents, including those with antithrombotic, PAF antagonist, and hypolipidemic properties.[1] Oxadiazoles are important bioisosters for esters and amides in drug discovery with reported muscarinic agonist, benzodiazepine receptor agonist, 5-HT agonist, and antirhinoviral activities.[2] However, the incorporation of isoxazole and oxadiazole heterocycles into a two-ring 5-isoxazol-4-yl-[1,2,4]oxadiazole system, which we believe could be a useful diheterocyclic agent with potential biological activities, has only been investigated synthetically by Neidlein in 1996.[3] We report here a novel solution-phase synthesis of the 5-isoxazol-4-yl-[1,2,4]oxadiazole diheterocycles (e.g., **I**) from nitrile oxide and alkynoate ester precursors, as well as the preparation of a small library of these compounds on solid phase (Scheme 1).

## Results and Discussion

**Development of a Solution-Phase Route to I.** The key intermediate in our synthetic strategy is isoxazole-substituted methyl ester **5**, prepared as outlined in Scheme 2. PMB-protection of 3-butyn-2-ol was prepared by deprotonation with sodium hydride in anhydrous THF at 0 °C followed by addition of *p*-methoxybenzyl chloride and TBAI (cat.).[4] A THF solution of the resulting *p*-methoxybenzyl-protected alkyne (**2**) was C-lithiated with *n*BuLi in hexane at −78 °C[5] and subsequently acylated with methyl chloroformate to give **3** ($R_1 = CH_3$). *o*-Chlorobenzaldehyde oxime **4a**, prepared from *o*-chlorobenzaldehyde hydroxylamine hydrochloride and sodium acetate in a mixture of ethanol and water, was comixed with alkynoate **3** in THF and treated with bleach at 0 °C.[6,7] This modified Huisgen method for in situ nitrile oxide formation delivered 3,4,5-trisubstituted isoxazole **5** in 70% yield.[7] Although strong steric ($\gamma$-branched moiety providing greater steric encumbrance than the carbomethoxy moiety) and weak electronic factors favor the formation of **5**, it is of interest that this is the only regioisomer obtained. The high regioselectivity was confirmed by the appearance of only one product in addition to unreacted starting material signals in the crude product $^1$H NMR. NOE difference $^1$H NMR experiments were performed to confirm the regiochemistry. Thus, irradiation of the methyl ester moiety in **5** produced NOE enhancement of all aromatic protons. This regioselectivity is also consistent with similar results reported by others.[8] We next performed the 1,3-dipolar cycloaddition on the methyl ester derivative from propargyl alcohol (see **3**; $R_1$

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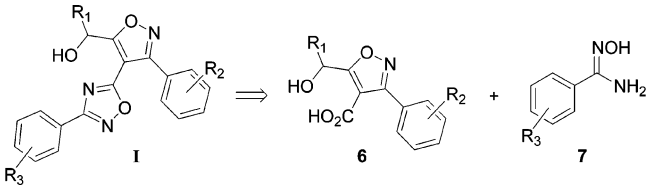
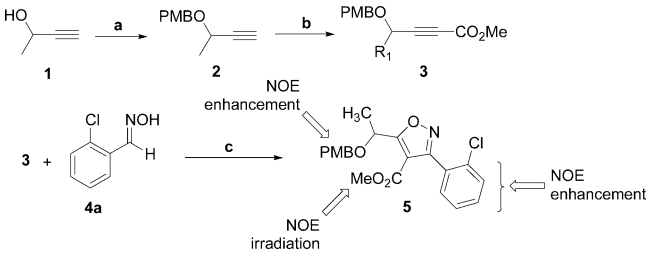
**SCHEME 1. 1,2,4-Oxadiazole Synthesis**

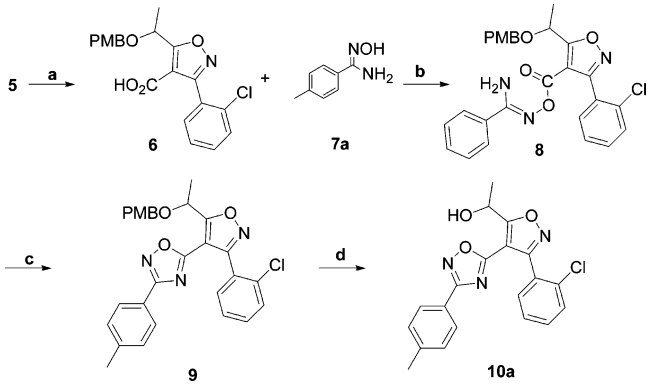


**SCHEME 2. Synthesis of Isoxazole-Substituted Methyl Ester Intermediate**[a]



[a] Reagents and conditions: (a) NaH, THF, 5 h; PMBCl, TBAI, 3 d. (b) *n*BuLi, anhydrous THF, −78 °C, 2 h; $ClCO_2Me$, −78 °C → rt, 5 h. (c) NaOCl, THF, 0 °C → rt, 3 d.

**SCHEME 3. Solution-Phase Synthesis of the 5-Isoxazol-4-yl-[1,2,4]oxadiazole System**[a]



[a] Reagents and conditions: (a) NaOH, $H_2O$, reflux, overnight; (b) EDC, 50 °C, overnight; (c) EDC, 115 °C, 3 h; (d) DDQ, DCM/$H_2O$ =18:1, rt, 5 h.

= H) and were pleased to again observe complete regioselectivity.

Saponification of cycloadduct **5** with refluxing aqueous sodium hydroxide (1.5 equiv) gave 4-carboxyisoxazole **6** (Scheme 3). Adapting Porco's two-step, one-pot condensation method,[9] benzamidoxime **7a**, readily prepared from the benzonitrile derivative and hydroxylamine hydrochloride in 95% ethanol, was O-acylated with **6**. Further dehydration of this *O*-acyl benzamidoxime (**8**) with additional 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) in refluxing 1,4-dioxane delivered the targeted [1,2,4]oxadiazole in 40% yield. Subsequent deprotection of the *p*-methoxybenzyl ether with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in methylene chloride/water (18:1) gave the 5-isoxazol-4-yl-[1,2,4]oxadiazole diheterocycle **10** in good yield (69%).[10]

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**Development of a Solid-Phase Route to I.** With this solution-phase route in hand, we set out to implement this strategy on solid phase. 3-Butyn-2-ol was loaded onto the trichloroacetimide derivative of Wang resin through the action of $BF_3{\cdot}OEt_2$ to give **11** ($R_1$ = $CH_3$), which was confirmed by the disappearance of the strong C=N stretching band at 1664 $cm^{-1}$.[11] To avoid deprotonation of the resin backbone in the alkyne acylation step, we used LDA instead of *n*BuLi to lithiate the resin-bound alkyne. Subsequent *C*-acylation with methyl chloroformate was accomplished overnight at room temperature (single bead FTIR, 1716 $cm^{-1}$ C=O). Nitrile oxide 1,3-dipolar cycloaddition to this resin-bound alkyne employed benzaldehyde oximes and proceeded smoothly with the aid of excess bleach (single bead FTIR, 1728 $cm^{-1}$ C=O). Lithium hydroxide in a mixture of water, methanol, and THF saponified the resin-bound methyl ester at room temperature to give the carboxylic acid substituted isoxazole (single bead FTIR, 1731 $cm^{-1}$ C=O) required for 1,2,4-oxadiazole formation. This chemistry plus Wang resin loaded with propargyl alcohol (**11**; $R_1$ = H) delivered a library of 18 5-isoxazol-4-yl-[1,2,4]oxadiazole compounds, by the two-step condensation of carboxylic acids **14** with various benzamidoxime derivatives (**14** → **15**) in the presence of excess EDC in DMF (see Table). The final products were released from the resin by treatment with 50% TFA in dichloromethane. Crude $^1H$ NMR of the resulting mixture shows that **16**, the consequence of incomplete carbomethoxylation of **11**, is the only identifiable side product of this chemistry. An NOE difference NMR experiment on compound **10a** ($R_1$ = $CH_3$ irradiation) confirmed that the solid-phase regioselectivity matched that of the solution phase.

In summary, a seven-step solid-phase synthesis of 5-isoxazol-4-yl-[1,2,4]oxadiazole diheterocyclics, which proceed through an alkynoate intermediate, has been developed. This work also reports the first library synthesis of this class of compounds on solid phase in good overall yield.

## Experimental Section[15]

**Solution-Phase Studies. 1-Methoxy-4-(1-methylprop-2-ynyl)oxymethylbenzene (2).** Marshall's method[4] was employed for the preparation of **2** from 3-butyn-2-ol (84% yield): $^1H$ NMR ($CDCl_3$) $\delta$ 1.45(d, 3H), 2.46(d, 1H), 3.8(s, 3H), 4.18(q, 1H), 4.44(d, 1H), 4.72(d, 1H), 6.89(d, 2H), 7.29(d, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 22.0, 55.3, 63.8, 70.1, 73.0, 83.8, 113.8, 129.7, 129.8, 159.3. This crude product was employed in the next step without further purification.

**Methyl 4-(4-Methoxybenzyloxy)pent-2-ynoate (3).** Alkyne **2** (1.6 g, 8.4 mmol) and anhydrous THF (25 mL) were placed in a 50-mL round flask under nitrogen at −78 °C and treated with *n*-BuLi in hexane (5.75 mL, 9.2 mmol, 1.6 M). The temperature was maintained at −78 °C for 2 h at which time $ClCO_2Me$ (0.87 g, 9.2 mmol) was added to the mixture slowly over 20 min. After stirring at room temperature for 5 h, the reaction was quenched by the addition of water, the solvent was removed, and the residue was dissolved in ether. After washing with water and brine, the ethereal layer was dried over $Na_2SO_4$ and concentrated by rotovaporation. Flash chromatography gave **3** (2 g, 8.1 mmol, 96%) as light yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.49(d, 2H), 3.81(d, 2H), 4.29(q, 1H), 4.44(d, 1H), 4.72(d, 1H), 6.89(d, 2H), 7.29(d, 2H); $^{13}C$ NMR

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**SCHEME 4. Solid-Phase Synthesis of 5-Isoxazol-4-yl-[1,2,4]oxadiazole Diheterocyclics**

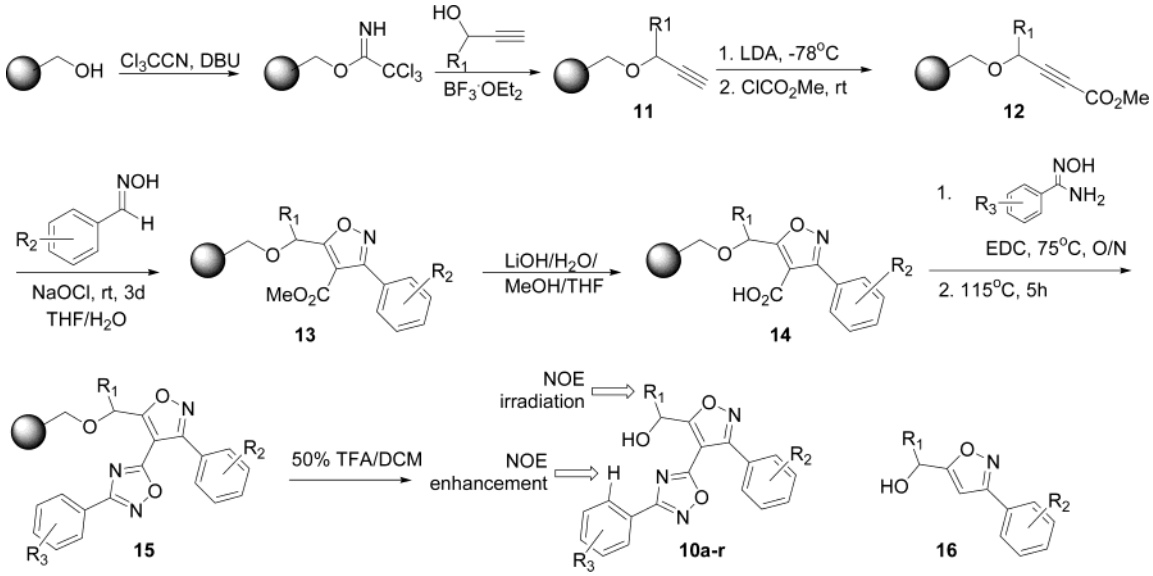


**TABLE 1. Oxadiazole-Substituted Isoxazoles Generated from Wang Resin**

| entry | product | $R_1$ | $R_2$ | $R_3$ | overall yield (%) |
|---|---|---|---|---|---|
| 1 | **10a** | $CH_3$ | *o*-Cl | *p*-$CH_3$ | 15 |
| 2 | **10b** | $CH_3$ | *o*-Cl | *p*-Cl | 8 |
| 3 | **10c** | $CH_3$ | *o*-Cl | *p*-OMe | 16 |
| 4 | **10d** | $CH_3$ | *p*-Cl | *p*-$CH_3$ | 12 |
| 5 | **10e** | $CH_3$ | *p*-Cl | *p*-Cl | 20 |
| 6 | **10f** | $CH_3$ | *p*-Cl | *p*-OMe | 13 |
| 7 | **10g** | $CH_3$ | *o*-OMe | *p*-$CH_3$ | 15 |
| 8 | **10h** | $CH_3$ | *o*-OMe | *p*-Cl | 13 |
| 9 | **10i** | $CH_3$ | *o*-OMe | *p*-OMe | 14 |
| 10 | **10j** | $CH_3$ | *p*-OMe | *p*-$CH_3$ | 23 |
| 11 | **10k** | $CH_3$ | *p*-OMe | *p*-Cl | 23 |
| 12 | **10l** | $CH_3$ | *p*-OMe | *p*-OMe | 27 |
| 13 | **10m** | H | *o*-OMe | *p*-$CH_3$ | 20 |
| 14 | **10n** | H | *o*-OMe | *p*-Cl | 20 |
| 15 | **10o** | H | *o*-OMe | *p*-OMe | 27 |
| 16 | **10p** | H | *p*-OMe | *p*-$CH_3$ | 20 |
| 17 | **10q** | H | *p*-OMe | *p*-Cl | 15 |
| 18 | **10r** | H | *p*-OMe | *p*-OMe | 7 |

($CDCl_3$) $\delta$ 21.2, 52.7, 55.2, 63.6, 70.7, 76.6, 87.2, 113.8, 129.2, 129.7, 153.7, 159.4.

**General Procedure for the Synthesis of Benzaldehyde Oximes (4).** Benzaldehyde (10 mmol) was added to hydroxylamine hydrochloride (1.39 g, 20 mmol) in water and ethanol (30 mL, 1:5) at 0 °C followed by the addition of sodium acetate (2.46 g, 30 mmol). The mixture was stirred at room temperature for 2 h at which time the ethanol was removed by rotovaporation. Water was added and the aqueous phase was extracted with DCM (2×). The combined organic layer was dried over $Na_2SO_4$ and concentrated to give the oxime products **4a**−**d**. 2-Chlorobenzaldehyde oxime (**4a**):[12] mp 68−69 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.26−7.35(m, 2H), 7.4(q, 1H), 7.81(q, 1H). 4-Chlorobenzaldehyde oxime (**4b**):[12] mp 96−97 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.38(d, 2H), 7.49(d, 2H), 8.11(s, 1H). 2-Methoxybenzaldehyde oxime (**4c**):[13] mp 90−91 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.87(s, 3H), 6.92(d, 1H), 6.97(t, 1H), 7.36(t, 1H), 7.66(d, 1H), 8.48(s, 1H), 8.67(s, 1H). 4-Methoxybenzaldehyde oxime (**4d**):[12] mp 48−49 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.83(s, 3H), 4.78(broad, 1H), 6.92(d, 2H), 7.54(d, 2H), 8.11(s, 1H).

**Methyl 3-(2-Chlorophenyl)-5-[1-(4-methoxybenzyloxy)-ethyl]isoxazole-4-carboxylate (5).** Methyl ester **3** (1.24 g, 5 mmol), 2-chlorobenzaldehyde oxime (**4a**; 0.86 g, 5.5 mmol), and THF (20 mL) were place in a round-bottom flask and cooled to 0 °C. Bleach (35 mL, 25 mmol, 5%) was added slowly through an addition funnel, and the mixture was stirred at room temperature for 3 d at which time the organic phase was separated from the reaction mixture and the aqueous phase was extracted with EtOAc (2×). The combined organic phase was dried over $Na_2SO_4$, and the solvent was removed to give the crude product, which was purified by flash chromatography to give **5** (1.39 g, 3.5 mmol, 70%) as a oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.65(d, 3H), 3.66(s, 3H), 3.78(s, 3H), 4.49(d, 2H), 5.32(q, 1H), 6.85(d, 2H), 7.25(d, 2H), 7.38−7.47(m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.8, 51.7, 55.1, 68.5, 71.6, 110.1, 113.7, 126.5, 128.0, 129.3, 129.5, 129.6, 130.9, 131.0, 133.8, 159.3, 160.3, 161.5, 176.9. Anal. Calcd for $C_{21}H_{20}ClNO_5$: C, 62.77; H, 5.02; N, 3.49. Found: C, 62.71; H, 4.99; N, 3.50.

**3-(2-Chlorophenyl)-5-[1-(4-methoxybenzyloxy)ethyl]-isoxazole-4-carboxylic Acid (6).** Isoxazole-substituted carboxylic acid methyl ester **5** (1.4 g, 3.5 mmol) in aqueous sodium hydroxide (0.21 g, 5.25 mmol) was refluxed at 105 °C overnight. The mixture was washed with EtOAc and the aqueous was then acidified with dilute aqueous HCl to pH 1. The resulting cloudy mixture was extracted with EtOAc, and this organic phase was dried over $Na_2SO_4$. Removal of the solvent gave the pure isoxazole-substituted carboxylic acid compound (0.98 g, 2.5 mmol, 72%) as a off-white solid without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 1.65(d, 3H), 3.77(s, 3H), 4.52-(s, 2H), 5.33(q, 1H), 6.84(d,2H), 7.26(d,2H), 7.36−7.46(m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.0, 55.2, 69.0, 72.0, 109.4, 113.8, 126.6, 127.6, 129.1, 129.5, 129.7, 130.9, 131.1, 133.9, 159.5, 160.6, 165.8, 178.3. Anal. Calcd for $C_{20}H_{18}ClNO_5 \cdot 1/2H_2O$: C, 60.54; H, 4.83; N, 3.53. Found: C, 61.10; H, 4.70; N, 3.64.

**General Procedure for the Synthesis of Benzamidoximes (7).** Triethylamine (3.2 mL, 23 mmol) was added to a mixture of benzyl nitrile (10 mmol) and hydroxylamine hydrochloride (1.5 g, 22 mmol) in 15 mL of 95% ethanol in water. The resulting solution was refluxed at 75 °C overnight. After the mixture cooled to room temperature, 15 mL of water was added and ethanol was removed by rotovap to precipitate product **7a**−**c**. *N*-Hydroxy-4-methyl-benzamidine (**7a**):[8] mp 136−137 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.38(s, 3H), 4.87(s, 2H), 7.24-(d, 2H), 7.52(d, 2H). *N*-Hydroxy-4-chloro-benzamidine (**7b**):[14] mp 128−129 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.88(broad, 2H), 7.38(d,

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2H), 7.57(d, 2H). *N*-Hydroxy-4-methoxy-benzamidine (**7c**):[14] mp 114−115 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.83(s, 3H), 4.83(broad, 2H), 6.92(d, 2H), 7.57(d, 2H).

**5-{3-(2-Chloro-phenyl)-5-[1-(4-methoxy-benzyloxy)-ethyl]-isoxazol-4-yl}-3-*p*-tolyl-[1,2,4]oxadiazole (9).** A mixture of isoxazole carboxylic acid **6** (390 mg, 1 mmol), benzamidoxime (180 mg, 1.2 mmol), and EDC (383 mg, 2 mmol) in 5 mL of 1,4-dioxane was stirred at 50 °C under nitrogen overnight. The reaction mixture was then heated to 115 °C for another 3 h. The crude product was purified by flash chromatography to give the pure compound (200 mg, 0.4 mmol, 40%) as an oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.76(d, 3H), 2.40(s, 3H), 3.66(s, 3H), 4.56-(q, 2H), 6.74(d,2H), 7.17(d,2H),7.26(d,2H),7.3−7.6(m, 4H), 7.87-(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.6, 21.5, 54.9, 68.0, 71.8, 104.6, 113.6, 123.3, 126.8, 127.0, 127.2, 127.3, 129.2, 129.4, 129.7, 131.3, 131.5, 133.9, 141.7, 159.2, 159.4, 168.0, 168.2, 175.2. Anal. Calcd for $C_{28}H_{24}ClN_3O_4 \cdot H_2O$: C, 64.68; H, 5.04; N, 8.08. Found: C, 65.13; H, 4.75; N, 8.14.

**PMB Deprotection to 1-[3-(2-Chloro-phenyl)-4-(3-*p*-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-ethanol (10a).** DDQ(136 mg, 0.6 mmol) was added to the solution of isoxazole-oxadiazole **9** (200 mg, 0.4 mmol) in 4.75 mL of DCM and water (18:1). After 5 h, the reaction mixture was filtered, and the pure product (105 mg, 0.28 mmol, 70%) was obtained by flash chromatography: mp 141−142 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.79-(d,3H), 2.40(s, 3H), 7.27(d, 2H), 7.35−7.51(m, 4H), 7.89(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.7, 12.6, 63.4, 103.8, 122.6, 126.7, 127.0, 127.3, 130.0, 131.3, 131.8, 134.0, 142.3, 159.9, 167.5, 168.9,-178.3. Anal. Calcd for $C_{20}H_{16}ClN_3O_3$: C, 62.91; H, 4.22; N, 11.01. Found: C, 63.12; H, 4.20; N, 10.92.

**Solid-Phase Studies. Trichloroacetimide Resin.** Wang resin (1.3 mmol/g, 1 g, 1.3 mmol) in dry dichloromethane was treated with trichloroaceonitrile (3.75 g, 26 equiv). After the mixture was cooled to 0 °C, DBU (158 mg, 1.04 mmol) was added slowly, and the reaction was stirred for 1 h. Single bead IR analysis showed complete disappearance of the hydroxy stretching band at 3500 cm$^{-1}$ of the Wang resin with appearance of a strong C═N signal at 1664 cm$^{-1}$.

**Resin-Bound Benzyl Ether (11).** The trichloroacetimide resin (1 g, 1.09 mmol) was treated with 3-butyn-2-ol (229 mg, 3.27 mmol) and a catalytic amount of $BF_3 \cdot OEt_2$. Ether formation was confirmed by the disappearance of C═N stretching band at 1664 cm$^{-1}$. The similar procedure was performed to obtain Wang resin bound propargyl alcohol.

**Resin-Bound 4-Hydroxy-2-pentynoic Acid Methyl Ester (12).** Resin-bound benzyl ether **11** (0.5 g, 0.61 mmol) was treated with LDA (0.9 mL, 1.8 mmol, 2.0 M in hexane) at −78 °C under nitrogen for 3 h. After slow addition of $ClCO_2Me$ (179 mg, 1.8 mmol), the reaction mixture was warmed to room temperature and stirred overnight: IR (neat) 1716 cm$^{-1}$.

**Resin-Bound Isoxazole Carboxylic Acid Methyl Ester (13).** Resin-bound 4-hydroxy-2-pentynoic acid methyl ester **12** (0.5 g, 0.57 mmol) was mixed with benzaldehyde oximes **4a**−**d** (1.71 mmol) in THF and then treated with excess bleach (8.6 mL, 5.7 mmol) for 3 d: IR (neat) 1728 cm$^{-1}$.

**Resin-Bound Isoxazole-Substituted Carboxylic Acid (14).** Resin-bound isoxazole-substituted carboxylic acid methyl ester **13** (0.5 g, 0.49 mmol) was treated with LiOH (58 mg, 2.4 mmol) in a mixture of water, methanol, and THF (1:1:3) at room temperature for 3 d. The resin was washed with MeOH and water, MeOH, DCM, MeOH, and DCM and then neutralized with dilute HCl in MeOH and THF (1:3): IR (neat) 1720 cm$^{-1}$.

(15) While we attempted to obtain elemental analysis data for all isolated compounds, the data for **3**, **10b**, **10c**, **10h**, **10i**, **10m**, **10p**, **10q**, and **10r** came back outside of the ±0.4% acceptable window. Fortunately, as evidenced by the corresponding $^1$H and $^{13}$C NMR data (see Supporting Information), these compounds are pure. We conclude that these compounds absorbed moisture during shipping and handling. Compound **8** is an un-isolated intermediate; therefore, elemental analyses are not reported.

**Resin-Bound Isoxazole-Oxadiazole Diheterocyclic Compounds (15).** Resin-bound isoxazole-substituted carboxylic acid **14** (0.5 g, 0.49 mmol) was treated with amidoximes **7a**−**c** (1.5 mmol) and EDC (0.48 g, 2.5 mmol) in DMF, and heated to 75 °C overnight. The mixture was then refluxed at 115 °C for another 5 h at which time the resin was washed thoroughly with DCM, MeOH, and DCM and dried under high vacuum pump.

**General Procedure for Resin Cleavage.** Resin with the desired 5-isoxazol-4-yl-[1,2,4]oxadiazole **15** was placed in a 10-mL polyethylene fritted tube and treated with 50% TFA in DCM for 2 h. The solution was drained from the tube, and the solvent was removed by rotovap. Flash chromatography with a mixture of hexane and ethyl acetate delivered the pure final diheterocyclic products.

**1-{3-(2-Chloro-phenyl)-4-[3-(4-chloro-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10b).** Mp 110−111 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.82(d, 3H), 5.40−5.49(m, 2H), 7.42−7.57(m, 6H), 7.96(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.7, 63.4, 103.6, 124.0, 126.7, 127.0, 128.7, 129.4, 130.0, 131.3, 131.9, 134.0, 138.1, 160.0, 166.8, 169.3, 178.4.

**1-{3-(2-Chloro-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10c).** Mp 113−114 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.82(d, 3H), 3.87(s, 3H), 5.41(q, 1H), 6.99(d,2H), 7.41−7.45(sex, 1H), 7.50−7.56(m, 3H),7.96(d,2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.7, 55.4, 63.5, 103.9, 114.4, 117.8, 126.7, 127.0, 129.1, 130.0, 131.3, 131.8, 134.0, 160.0, 162.4, 167.2, 168.8, 178.2.

**1-[3-(4-Chloro-phenyl)-4-(3-*p*-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-ethanol (10d).** Mp 129−130 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.79(d,3H), 2.44(s, 3H), 5.372(q, 1H), 5.58(d, 1H), 7.31(d, 2H), 7.51(d, 2H), 7.64(d, 2H), 7.92(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.5, 21.6, 63.3, 102.3, 122.5, 125.5, 127.4, 129.0, 129.8, 130.6, 137.0, 142.5, 160.9, 167.7, 169.1, 179.2. Anal. Calcd for $C_{20}H_{16}ClN_3O_3$: C, 62.91; H, 4.22; N, 11.01. Found: C, 62.72; H, 4.09; N, 10.67.

**1-{3-(4-Chloro-phenyl)-4-[3-(4-chloro-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10e).** Mp 159−160 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.80(d, 2H), 5.26(d, 1H), 5.40(q, 1H), 7.49−7.52(m, 4H), 7.63(d, 2H), 7.98(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.6, 63.3, 102.1, 123.9, 125.4, 128.7, 129.0, 129.5, 130.6, 137.0, 138.2, 160.9, 167.0, 169.4, 179.2. Anal. Calcd for $C_{19}H_{13}Cl_2N_3O_3$: C, 56.74; H, 3.26; N, 10.45. Found: C, 56.86; H, 3.24; N, 10.24.

**1-{3-(4-Chloro-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10f).** Mp 153−154 °C; $^1$H NMR ($CDCl_3$) $\delta$1.79(d, 3H), 3.88(s, 3H), 5.37(q, 1H), 5.60(d, 1H), 7.01(d, 2H), 7.51(d, 2H), 7.64(d, 2H), 7.68(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.5, 55.4, 63.3, 102.4, 114.5, 117.7, 125.5, 129.0, 130.6, 136.9, 160.9, 162.4, 167.4, 168.9, 179.1. Anal. Calcd for $C_{20}H_{16}ClN_3O_4 \cdot 1/2H_2O$: C, 59.78; H, 4.21; N, 10.33. Found: C, 59.48; H, 4.13; N, 10.23.

**1-[3-(2-Methoxy-phenyl)-4-(3-*p*-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-ethanol (10g).** Mp 184−185 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.69(d, 3H), 2.34(s, 3H), 3.55(s,3H), 5.27(q, 1H), 5.68-(broad, 1H), 6.92(d, 1H), 7.00(t, 1H), 7.21(d, 2H), 7.42(d, 2H), 7.84(d,2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.6, 21.6, 55.2, 63.3, 103.9, 110.0, 114.2, 116.3, 120.7, 122.8, 127.3, 129.7, 130.6, 132.1, 142.1, 157.5, 159.5, 167.3, 169.8, 177.6. Anal. Calcd for $C_{21}H_{19}N_3O_4$ : C, 66.83; H, 5.07; N, 11.13. Found: C, 66.84; H, 5.00; N, 10.98.

**1-[4-[3-(4-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(2-methoxy-phenyl)-isoxazol-5-yl]-ethanol (10h).** $^1$H NMR ($CDCl_3$) $\delta$ 1.79(d, 3H), 3.65(s, 3H), 5.36(broad, 1H), 5.48(broad, 1H), 7.02(d, 1H), 7.10(t, 1H), 7.48−7.56(m, 4H), 7.98(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.6, 55.3, 63.4, 103.9, 111.1, 116.2, 120.8, 124.1, 128.7, 129.4, 130.7, 132.3, 138.0, 157.5, 159.6, 166.6, 170.2, 177.5.

**1-{3-(2-Methoxy-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10i).** $^1$H NMR ($CDCl_3$) $\delta$ 1.80(d, 3H), 3.65(s, 3H), 3.88(s, 3H), 5.38(q, 1H), 5.79(d, 1H), 6.99−7.02(m, 3H), 7.09(sex, 1H), 7.50−7.55(m, 2H), 7.97(d,

2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.6, 55.3, 55.4, 63.5, 104.1, 111.1, 114.5, 116.1, 117.8, 120.8, 129.1, 130.7, 132.2, 157.5, 159.6, 162.3, 167.0, 169.7, 177.6.

**1-[3-(4-Methoxy-phenyl)-4-(3-p-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-ethanol (10j).** Mp 131−132 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.78(d,3H), 2.43(s, 3H), 3.88(s, 3H), 7.03(d, 2H), 7.31-(d, 2H), 7.64(d, 2H), 7.93(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.9, 22.0, 31.3, 55.7, 63.6, 102.5, 114.3, 119.3, 122.9, 127.5, 130.0, 130.9, 142.5, 161.5, 161.6, 167.8, 169.6, 179.0. Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 67.19; H, 5.09; N, 11.10.

**1-[4-[3-(4-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-isoxazol-5-yl]-ethanol (10k).** Mp 121−122 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.79(d, 3H), 3.89(s, 3H), 5.38(q, 1H), 5.46(broad, 1H), 7.04(d, 2H), 7.49(d, 2H), 7.62(d, 2H), 7.99-(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.5, 55.4, 63.4, 102.2, 114.1, 118.9, 123.9, 128.7, 129.5, 130.6, 138.1, 161.4, 161.5, 166.9, 169.8, 178.8. Anal. Calcd for $C_{20}H_{16}ClN_3O_4$: C, 60.39; H, 4.05; N, 10.56. Found: C, 60.01; H, 3.96; N, 10.29.

**1-{3-(4-Methoxy-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-ethanol (10l).** Mp 112−113 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.78(d, 3H), 3.87(s, 3H), 3.88(s, 3H), 6.99−7.04(m, 4H), 7.63(d, 2H), 7.98(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.5, 55.4, 55.5, 63.3, 102.3, 114.1, 114.5, 117.8, 119.1, 129.1, 130.7, 161.4, 161.5, 162.4, 167.3, 169.4, 178.9. Anal. Calcd for $C_{21}H_{19}N_3O_5 \cdot H_2O$: C, 62.68; H, 5.01; N, 10.44. Found: C, 62.56; H, 4.68; N, 10.25.

**[3-(2-Methoxy-phenyl)-4-(3-*p*-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-methanol (10m).** Mp 118−119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.43(s, 3H), 3.65(s, 3H), 5.09(d, 1H), 5.24(q, 1H), 7.02(d, 1H), 7.10(t, 1H), 7.31(d, 2H), 7.52(d, 2H), 7.93(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.6, 55.3, 56.5, 105.4, 111.1, 116.2, 120.7, 122.8, 127.3, 129.7, 130.7, 132.2, 142.2, 157.5, 159.3, 167.5, 169.7, 174.7.

**[4-[3-(4-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(2-methoxy-phenyl)-isoxazol-5-yl]-methanol (10n).** Mp 162−163 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.65(s, 3H), 5.11(s, 2H), 5.18(broad, 1H), 7.02(d, 1H), 7.11(t, 1H), 7.48−7.54(m, 4H), 7.98(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.3, 56.5, 105.2, 111.1, 116.1, 120.8, 124.2, 128.7, 129.4, 130.7, 132.3, 138.0, 157.5, 159.4, 166.8, 170.0, 174.7. Anal. Calcd for $C_{19}H_{14}ClN_3O_4$: C, 59.46; H, 3.68; N, 10.95. Found: C, 60.00; H, 3.72; N, 10.85.

**{3-(2-Methoxy-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-methanol (10o).** Mp 155−156 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.66(s, 3H), 3.88(s, 3H), 5.08(d, 1H), 5.20(q, 1H), 7.00−7.03(m, 3H), 7.10(t, 1H), 7.51−7.55(m, 2H), 7.98(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.5, 55.7, 56.8, 105.7, 111.3, 114.7, 116.5, 118.3,121.0, 129.3, 130.9, 132.5, 157.8, 159.6, 162.6, 167.4, 169.8, 175.0. Anal. Calcd for $C_{20}H_{17}N_3O_5 \cdot 1/2H_2O$: C, 61.85; H, 4.67; N, 10.82. Found: C, 62.23; H, 4.67; N, 10.60.

**[3-(4-Methoxy-phenyl)-4-(3-p-tolyl-[1,2,4]oxadiazol-5-yl)-isoxazol-5-yl]-methanol (10p).** Mp 182−183 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.44(s, 3H), 3.89(s, 3H), 5.07(s, 2H), 7.04(d, 2H), 7.32-(d, 2H), 7.68(d, 2H), 7.94(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.6, 55.4, 56.5, 103.7, 114.1, 119.0, 122.6, 127.4, 129.8, 130.7, 142.4, 161.3, 161.5, 167.8, 169.4, 176.2.

**[4-[3-(4-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-isoxazol-5-yl]-methanol (10q).** Mp 176−177 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.89(s,3H), 5.8(s, 2H), 7.05(d, 2H), 7.50-(d, 2H), 7.67(d,2H), 7.99(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.4, 56.5, 114.2, 118.8, 124.0, 128.3, 128.7, 129.5, 130.7, 138.1, 161.3, 161.6, 167.1, 169.7, 176.2.

**{3-(4-Methoxy-phenyl)-4-[3-(4-methoxy-phenyl)-[1,2,4]-oxadiazol-5-yl]-isoxazol-5-yl}-methanol (10r).** Mp 173−174 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.88(S, 3H), 3.89(s,3H), 5.06−5.15(m, 2H), 7.01−7.06(m, 4H), 7.68(d, 2H), 7.99(d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.3, 55.5, 56.5, 103.7, 114.1, 114.5, 117.8, 119.0, 129.1, 130.7, 161.3, 161.5, 162.4, 167.5, 169.3, 176.1.

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR for compounds **3**, **10b**, **10c**, **10h**, **10i**, **10m**, **10p**, **10q**, and **10r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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